

VU Research Portal

Late onset Alexander's disease presenting as cerebellar ataxia associated with a novel mutation in the GFAP gene

Schmidt, S.; Wattjes, M.P.; Gerding, W.M.; van der Knaap, M.S.

published in

Journal of Neurology

2011

DOI (link to publisher)

[10.1007/s00415-010-5849-0](https://doi.org/10.1007/s00415-010-5849-0)

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Schmidt, S., Wattjes, M. P., Gerding, W. M., & van der Knaap, M. S. (2011). Late onset Alexander's disease presenting as cerebellar ataxia associated with a novel mutation in the GFAP gene. *Journal of Neurology*, 258(5), 938-940. <https://doi.org/10.1007/s00415-010-5849-0>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

Late onset Alexander's disease presenting as cerebellar ataxia associated with a novel mutation in the *GFAP* gene

Stephan Schmidt · Mike P. Wattjes ·
Wanda M. Gerding · Marjo van der Knaap

Received: 17 August 2010 / Accepted: 22 November 2010 / Published online: 17 December 2010
© Springer-Verlag 2010

Sirs,

Alexander's disease (AD) is a rare genetic disorder caused by mutations in the glial fibrillary acid protein (GFAP) gene characterized by a relentlessly progressive neurological decline in children and infants. In contrast, the clinical course of adult onset forms of AD (AOAD) is usually more protracted and the clinical presentations vary widely. Here we present a case of late onset cerebellar ataxia with marked atrophy of the lower brain stem and the medulla on magnetic resonance imaging (MRI). Molecular genetic analysis revealed a novel missense mutation (c. 1148C > T, p. T383I) in the *GFAP* gene further broadening the spectrum of clinical and MRI presentations of AOAD.

S. Schmidt (✉)
Neurologische Gemeinschaftspraxis Bonn,
Kölustr. 480, 53117 Bonn, Germany
e-mail: schmidt@neurologie-in-bonn.de

S. Schmidt
Department of Neurology, Ruhr-Universität Bochum,
Knappschafts-Krankenhaus Langendreer,
In der Schornau 23–25, 44892 Bochum, Germany

M. P. Wattjes
Department of Radiology, MS and Alzheimer Center,
VU University Medical Center, De Boelelaan 1117,
1081 HV Amsterdam, The Netherlands

W. M. Gerding
Department of Human Genetics, Ruhr-Universität Bochum,
Building MA 5, Universitätsstr. 150, 44801 Bochum, Germany

M. van der Knaap
Department of Child Neurology, VU University Medical Center,
De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

AD is a rare leukodystrophy caused by mutations in the *GFAP* gene, typically affecting infants and children [1]. Nearly all AD mutations involve amino acid substitutions, and a dominant toxic or gain-of-function effect for mutant GFAP protein was hypothesized [2, 3]. While AD in infants and children typically presents with psychomotor retardation, seizures, ataxia and progressive spasticity leading to death within a few years [1, 2], clinical phenotypes with AOAD vary considerably and the clinical course is more protracted [4–6]. MRI criteria have been proposed for the diagnosis of AD [7]. However, more recent case series of patients with AOAD involving individuals with atypical clinical and MRI features not fully meeting the above diagnostic criteria, suggest that the spectrum of clinical phenotypes of AOAD may be broader than previously expected [4–6, 8].

A 65 year old otherwise healthy female of Caucasian origin presented with a 10 year history of slowly progressive unsteadiness of gait and slurred speech. On neurological examination, she revealed hypermetric horizontal saccades. There was moderate cerebellar dysarthria but no dysphagia or palatal myoclonus. Limb movements were hypermetric with moderate intention tremor. Reflexes of the legs were brisk, but plantar responses were flexor and there were no signs of spasticity. The gait was broad-based, ataxic. Sensory testing was normal for all modalities. There was no evidence of cognitive impairment. The family history revealed that the patient's father had a tremor and impaired taste with onset after the age of 70. Both grandmothers allegedly suffered from multiple sclerosis. All of her four children showed no signs of neurological impairment.

Previous genetic work-up including testing for spinocerebellar ataxia (SCA)-1, -2, -3, -6, -10, and -17 had revealed no abnormalities. Vitamins E and B₁₂ deficiency

had been ruled out as well. Enzyme activity of arylsulfatase A and β -galactocerebrosidase in leukocytes as well as concentrations of very long chain fatty acids and their respective ratios were normal. The cerebrospinal fluid contained 1 cell/ μ l, and oligoclonal bands were absent.

Axial T2-weighted MR images of the infratentorial brain region (a, b, c) demonstrate the severe atrophy of the brain stem, particularly of the medulla oblongata, and upper spinal cord (b, c, open arrows). Within the atrophic brain stem linear high T2 signal abnormalities of the cortico-spinal tract can be observed (a, small arrows). In addition, bilateral abnormalities affecting the hilus of the dentate nucleus are present (a, large arrows). The sagittal fluid-attenuated inversion-recovery image (d) shows the severe atrophy of the medulla oblongata and upper cervical spinal cord (open arrows) in combination with severe cerebellar atrophy. Axial T2-weighted images of the supratentorial regions (e, f) demonstrate bilateral signal abnormalities of the globus pallidus (large arrows). The MRI findings are shown in Fig. 1.

The nine exons and adjacent intronic regions of the *GFAP* gene (NM_002055 and alternative exon eight transcript NM_001131019) were PCR amplified (primer sequences available on request) and directly sequenced. A missense mutation (c. 1148C > T, p. T383I; positions

according to RefSeq NM_002055) was detected in exon seven in heterozygous state. This mutation results in an amino acid exchange on position 383 from threonine to isoleucine and a loss of a predicted phosphorylation site [9]. In silico analysis revealed that this sequence alteration is “probably damaging” using the polymorphism phenotyping tool [9] or “damaging” using the “sorting intolerant from tolerant (SIFT)” tool [10]. A cohort of 181 ethnically matched healthy German blood donors was screened for the mutation by PCR followed by differential enzymatic restriction with *Bgl*III in order to further examine the functional significance of this mutation. The presence of the C > T transition at this position was not detected in any of the 362 tested control chromosomes.

More than 60 different mutations within the coding region of *GFAP* have been identified in association with AD [1] but only few studies have systematically investigated *GFAP* mutations in AOAD [4]. The differential diagnosis of adult onset cerebellar ataxia involves a wide spectrum of disorders including SCA, autosomal recessive ataxias such as Friedreich’s ataxia, X-linked cerebellar ataxias such as ataxia teleangiectasia and fragile X-associated tremor/ataxia syndrome (FXTAS), abetalipoproteinemia, Refsum disease, late-onset GM2 gangliosidosis, cerebrotendinous xanthomatosis, autosomal dominant

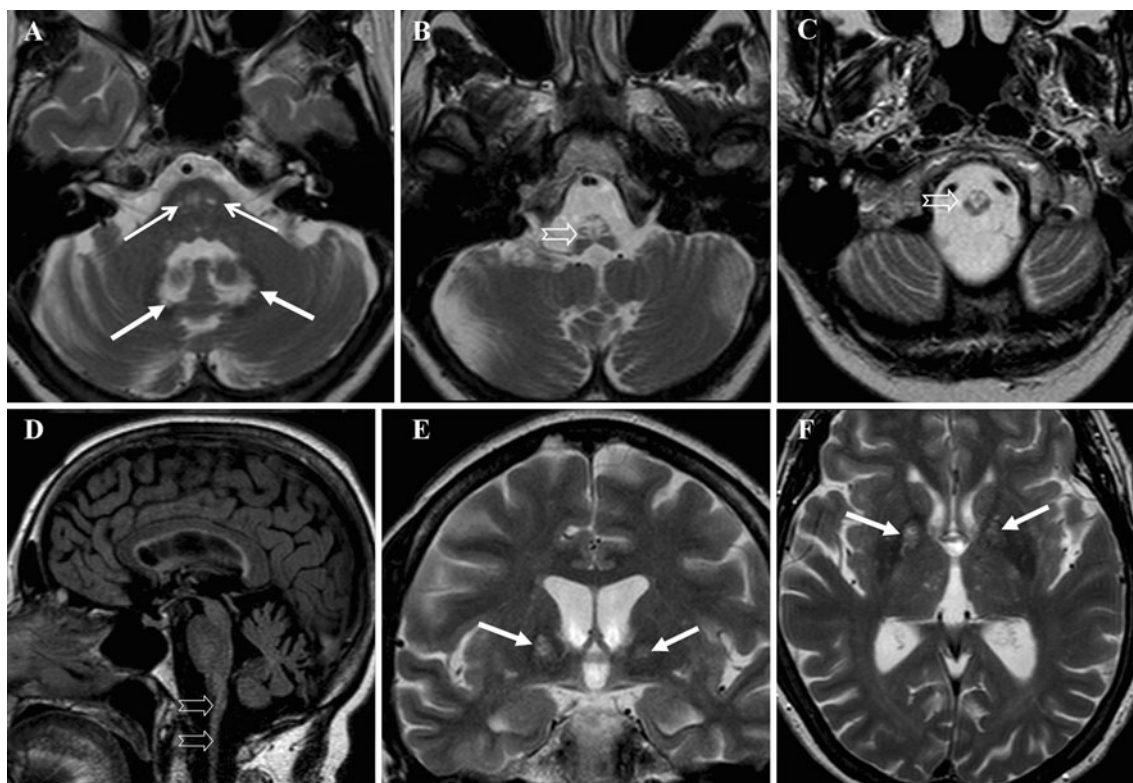


Fig. 1 MRI findings in a 65 year old woman with a novel missense mutation (c. 1148C > T, p. T383I) in the *GFAP* gene. The details are outlined in the text

mitochondrial heredoataxias as well as multisystem atrophy, vitamin B₁₂ and vitamin E deficiencies, primary progressive multiple sclerosis and adult manifestations of leukodystrophies [10–12]. The present case report highlights the importance of MR imaging in the differential diagnosis of adult onset leukodystrophies. Although our patient met only three out five MRI criteria for AD [7], the severe atrophy of the medulla oblongata along with signal abnormalities in the hilus of the dentate nucleus were suggestive of AOAD [5, 6, 8]. However, the symmetrical signal abnormalities of the globus pallidus on T2-weighted images are only rarely seen in AOAD [5, 6, 8].

In accordance with previous reports of AOAD, clinical progression in our patient was relatively slow compared with that seen in childhood onset of AD [1, 4–6]. In summary, sequencing of the *GFAP* gene should be considered in cases of late onset cerebellar ataxia, in particular in the presence of MRI findings compatible with AD. The spectrum of clinical and MRI phenotypes of AOAD may still be broader than previously anticipated.

References

1. Rodriguez D, Gauthier F, Bertini E et al (2001) Infantile Alexander disease: spectrum of GFAP mutations and genotype–phenotype correlation. *Am J Hum Genet* 69:1134–1140
2. Li R, Johnson AB, Salomons G et al (2005) Glial fibrillary acidic protein mutations in infantile, juvenile, and adult forms of Alexander disease. *Ann Neurol* 57:310–326
3. Quinlan RA, Brenner M, Goldman JE, Messing A (2007) GFAP and its role in Alexander disease. *Exp Cell Res* 313:2077–2087
4. Pareyson D, Fancellu R, Mariotti C et al (2008) Adult-onset Alexander disease: a series of eleven unrelated cases with review of the literature. *Brain* 131:2321–2331
5. Van der Knaap MS, Salomons GS, Li R et al (2005) Unusual variants of Alexander's disease. *Ann Neurol* 57:327–338
6. van der Knaap MS, Ramesh V, Schiffmann R et al (2006) Alexander disease: ventricular garlands and abnormalities of the medulla and spinal cord. *Neurology* 66:494–498
7. Van der Knapp MS, Naidu S, Breiter SN et al (2001) Alexander disease: diagnosis with MR imaging. *Am J Neuroradiol* 22:541–552
8. Farina L, Pareyson D, Minati L et al (2008) Can MR imaging diagnose adult-onset Alexander disease? *Am J Neuroradiol* 29:1190–1196
9. Sunyaev S, Ramensky V, Koch I, Lathe W 3rd, Kondrashov AS, Bork P (2001) Prediction of deleterious human alleles. *Hum Mol Genet* 10:591–597
10. Ng PC, Henikoff S (2001) Predicting deleterious amino acid substitutions. *Genome Res* 11:863–874
11. Abele M, Bürk K, Schöls L et al (2002) The aetiology of sporadic adult-onset ataxia. *Brain* 125:961–968
12. Wardle M, Majounie E, Muzaimi MB et al (2009) The genetic aetiology of late-onset chronic progressive cerebellar ataxia. A population-based study. *J Neurol* 256:343–348